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Revealed: NIH Funded Research at Wuhan Lab to Create Mutant Bat Coronaviruses and Study Their Capacity to Infect Humans

Records released by EcoHealth Alliance detail the datelined revelations of NIH-funded work on gain-of-function research on coronaviruses that was conducted by the Wuhan Institute of Virology (WIV) in China to create mutant viruses "to better predict the capacity of SARS-CoV-like coronaviruses to infect people."

Eco Health Alliance planned to engineer the spike protein from coronaviruses found in bats and put them into a backbone of a coronavirus found in mice.

Specific lines of research that proposed to conduct "gain of function" studies included:

- "We will test our models of host-range & emergence potential experimentally using reverse genetics, pseudovirus and receptor binding assays, and in vivo infection experiments in cell culture and humanized mice.

- "With bat CoVs that were isolated or sequenced in the field, we will identify receptor binding domains, model receptor use & binding, predict host range & emergence potential, and test & characterize receptor use and infectivity in vitro and in vivo using BSL-3 and humanized mice.

- "We will do this by sequencing the spike (or host-range receptor binding domain) protein gene from all or bat CoVs, creating mutants to identify how changes in sequence affect receptor use, and then test the most novel SARS-CoV-like CoV mutants' in vitro potential and risk."

In the continuing discussion of the aims of the research, the report states:

"In vitro characterization of CoV host-range & humanized mouse models We have developed primary cell lines and transformed cell lines from 9 bat species representing 5 genera of bat CoVs, and have established reverse genetics systems for 3 coronavirus species. We have also established a mouse model of SARS-CoV pathogenesis.

"We also have a large number of cell lines from humans and animals that we will use for cross-infectivity assays. We have obtained a panel of mAbs from Dr. Ralph Baric, who is keen to collaborate with us initially to test infectivity in his humanized mouse model and our BatCoV panel of pseudoviruses. We will also collaborate with Dr. Wuze Ren at the Wuhan Institute of Virology.

"This results will provide information whether bat CoVs could jump between species like SARS-CoV or MERS-CoV in nature. Current concern is low, and allows us to determine critical host-range factors and the potential for these viruses to infect humans directly, rather than through an intermediate species."

EcoHealth Alliance's $3.1 million grant to fund a project titled "Understanding the Risk of Bat Coronavirus Emergence" was awarded by the NIH on September 30, 2014. The Five Thirty Eight Interactive Site Location" is the PI.

Three online Chinese sites Nebei Daxi China Normal University in Shanghai, Yunnan Institute of Endemic Disease Control and Prevention and the Guangdong Center for Disease Control and Prevention of Guangdong in Guangzhou.

On May 27, 2016 the NIH awarded EcoHealth Alliance $598,709 over two years for the project titled "Understanding the Risk of Bat Coronavirus Emergence."

As EcoHealth Alliance grant application, reviewed by the NIH in June 2015, it is identified as a "Potentially Pandemic Pathogen" including Shi Zhengli and Zhang Yun-Zhi from the Wuhan Institute of Virology, Peter Daszak from EcoHealth Alliance, Linfa Wang from the University of the Chinese CDC and Preventive Medicine Guangdong Province."

A section of the EcoHealth Alliance application titled "EcoHealth Alliance Budget Justification" describes some of the work to be conducted by EcoHealth scientists in China:

"A research scientist will be hired at 12 months time per year to provide laboratory support for the project, including ordering supplies, shipping equipment and logistics, and coordinate animal and human sample shipments to the labs in China and in the U.S.

"Travel to China: Two trips to the Wuhan Institute of Virology in Yr 2 and Yr 3 (Travel) We will have three individuals from China (provincial CDC's and Wuhan Institute of Virology) travel to the U.S. in each of Years 2 and 4 and Yr 3 (Travel) and Yr 4 (Visitors). These individuals will be responsible for the approved human sampling as well as maintaining cold chain for storage and shipping samples.

"Dr. Zhengli Shi, Senior Virologist, Wuhan Institute of Virology, will work with the PI (Principal Investigator) (Consultancy)."

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In a budget calculation for the year 2014-15, the NIH as a sub-awardee of the Wuhan Institute of Virology to receive $128,716 in direct costs and $76,584 in indirect costs for a total of $205,300.

The salaries of Shi Zhengli and a WIV colleague Cai Yingyi are redacted from the budget. Even the first years of the grant, the funds to be received are $199,815.

A section of the grant award titled "Wuhan Institute of Virology Budget justification, Subaward" discusses "Other Direct Costs":

- Wild excursions

- We will be running PCR amplicons for 1,500 bats per year three samples per bat and will need to run each per … Extracted RNA per animal will be needed.

- DNA Sequencing

- Each year of the project: DNA sequencing will be performed on 1,200 samples at a cost of $2.50 per reaction …

- Laboratory Supplies

We request support for in vitro infection experiments using pseudoviruses carrying the spike proteins (wild type or mutants) or live viruses in cell lines of different origins, binding affinity assays between the spike proteins (wild type or mutants) and different cellular receptor molecules and receptor entry assays.

The Year 2 annual report for the coronavirus project, budget period Year 2, 2016 to May 31, 2017, under "Specific Aim 2," states:

"Evening predictions of CoV inter-species transmission. The following experiments will be undertaken in Year 2:

- Humanized mice with human ACE2 receptors will be infected with WIV1 and the two mutant chimeric MERS-like coronaviruses to determine the tissue tropism and pathogenicity of Task 3.1.G2.

- Mice infected with WIV1 and SHC014 at 10 LD50 in pseudovirus will be used in vitro cells of different origin in expressing different receptor molecules. Spillover potential for each isolated virus will be assessed.

- An infectious clone of SARS-like WIV1-CoV will be generated and used to evaluate the in vivo fitness cost of different RBD mutations. Furthermore, cross-infectivity of different MERS-related viruses identified from Chinese bats in the chimeric viruses with S gene of MERS-CoV will be evaluated in human DPP4 knock-in mice. Reverse genetics system will be constructed to study the receptor usage and infectivity of MERS-related coronaviruses.

Among the "Additional Year 2 items for Specific Aim 2" are:

- The infectious clone of WIV1 was successfully constructed using reverse genetics system.

- Two chimeric bat SARSr-like coronavirus strains were constructed by replacing the S [spike] gene in the backbone of WIV1.

- Work with the chimeric virus indicates that the receptor has been conserved, so as to conduct the experimental infection proposed in our BSL-3 facility.

The annual report submitted for Year 3 of the grant project, budget period runs 1, 2017 to May 31, 2018, under the heading "Specific Aim 2, Task 3.2 Testing of CoV inter-species transmission," notes:

"In Year 3, we successfully isolated WIV1 from the single (bat) fecal sample. Using the reverse genetics system we previously developed, we generated the infectious clone of WIV1. The infectivity of rescued virus in the S-gene gene of WIV1 and HeLa-hACE2 cells.

"Two SL-wiv sets were resequenced infected with WIV1, WIV1-N501Y and WIV1-N317L, and efficient virus replication was detected by immunofluorescence assay in all infections.

"To assess the usage of human ACE2 by the three novel SL-CoVs, we conducted virus infectivity studies using HeLa cells with or without the expression of human ACE2. All viruses replicated efficiently in the human ACE2-expressing cells."

In the Year 4 annual report, budget period June 1, 2018, to May 31, 2019, under the heading "Specific Aim 2, Task 3.2 Testing of CoV inter-species transmission," it states:

"The annual report submitted for Year 5 of the grant project, budget period runs 1, 2019 to May 31, 2020, under the heading "Specific Aim 2, Task 3.2 Testing of CoV inter-species transmission," notes:

"In Year 5, we successfully isolated WIV16 from the single (bat) fecal sample. Using the reverse genetics system we previously developed, we generated the infectious clone of WIV16. The infectivity of rescued virus in the S-gene gene of WIV16 and HeLa-hACE2 cells.

"Two SL-wiv sets were resequenced infected with WIV16, WIV1-WIV16 and WIV1-WIV16, and efficient virus replication was detected by immunofluorescence assay in all infections.

"To assess the usage of human ACE2 by the three novel SL-CoVs, we conducted virus infectivity studies using HeLa cells with or without the expression of human ACE2. All viruses replicated efficiently in the human ACE2-expressing cells."

In the Year 4 annual report, budget period June 1, 2018, to May 31, 2019, under the heading "Specific Aim 2, Task 3.2 Testing of CoV inter-species transmission," it states:

"Accomplishments for the last budget period. Specific aims, as listed in the original statement of work. Task 3.2 Testing of CoV inter-species transmission. Major activities, accomplishments and findings. Purpose. Major activities. Describe briefly what you did during the project period. Identify the number of times an activity was accomplished and/or a description of the activity performed. Describe significant activities not mentioned in the previous two categories. Findings. Significant results, including negative findings, and other findings or observations during the project period. A discussion of the significance of these results and their impact on the project or program and other expected outcomes.

"Key outcomes or other achievements. Describe the major outputs or outcomes (achievements) resulting from the project during this reporting period. Training and development. Describe how the project trained or developed the professional skills of project participants during this reporting period. Institutional development. Describe any project activities that improved the institutional infrastructure during this reporting period. Technology transfer. Describe technology transfer activities during this reporting period."

Under the heading "Publications, conference papers, and presentations," it states:

"Publications. Publications resulting from the project during this reporting period. Publications submitted but not published. Publications planned but not submitted. Publications resulting from previous periods that were not reported on

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